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COMPLETE SPECIFICATION

Manufacture of New Pyridine and Piperidine Compounds

We, SOCIETY OF CHEMICAL INDUSTRY IN BASLE (also known as GESELLSCHAFT FÜR CHEMISCHE INDUSTRIE IN BASEL), a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the nature of this invention and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

According to this invention new pyridine or piperidine compounds are made by condensing a monoaryl-acetonitrile containing at least one hydrogen atom in the acetonitrile residue with a pyridine or piperidine compound halogenated in the nucleus, in the presence of a metal or metal compound capable of eliminating halogen hydride, and, if desired, replacing by an alkyl residue a hydrogen atom attached to the carbon atom to which the nitrile group is connected. If desired, the nitrile group in the resulting compound may be converted into a carboxyl or an ester, amide, keto or methylene-amino group in one or more stages by a known method as hereinafter defined, a resulting pyridine compound may be converted into the corresponding piperidine compound by means of a reducing agent described in the literature as being suitable for hydrogenating the pyridine nucleus, and/or further substituents may be introduced as hereinafter described into the resulting pyridine or piperidine compound at the nitrogen atom in the ring.

The monoaryl-acetonitrile used for the reaction may contain a substituent in the methylene group of the acetonitrile residue, and also one or more substituents in the aryl residue. There may be mentioned, for example, phenyl-acetonitrile, naphthyl - acetonitrile, α-phenyl-α-alkyl-acetonitriles such as α-phenyl-α-methyl-acetonitrile, 3 - methoxyphenyl - acetonitrile, 3:4-dimethoxyphenyl-acetonitrile and 3:4 - methylenedioxyphenyl - acetonitrile. As pyridine and piperidine compounds halogenated in the nucleus there may be used, for example, 2-chloropyridine, 4-chloropyridine or 1-methyl-3-chloropiperidine. These compounds may also contain further substituents; thus 2-chloro-5-nitropyridine may be used as starting material. The reaction is advantageously conducted in an inert solvent, for example, ether, benzene or toluene. For the elimination of halogen hydride there is advantageously used sodium, potassium or lithium either as such or in the form of an amide, hydride, alcoholate or hydrocarbon compound thereof, for example, sodamide, sodium hydride, potassium tertiary butylate, potassium tertiary amylate, lithium butyl, sodium phenyl or lithium phenyl.

When by this reaction acetonitriles are obtained which still contain a hydrogen atom attached to the carbon atom to which the nitrile group is connected, this hydrogen atom may be replaced by an alkyl residue, for example by reaction with an alkyl halide, such as methyl chloride, ethyl chloride or diethylaminoethyl chloride in the presence of an agent capable of eliminating halogen hydride.

In preparing the acids and their amides and esters and the corresponding ketones and amines, from the α-aryl-α-piridyl-acetonitriles and α-aryl-α-piperidyl-acetonitriles obtained in the reaction, known methods for the conversion of a nitrile group into a carboxyl-, ester-, amide-,

keto or methyleneamino-group are used. The term " known methods " is here used to denote methods described in the literature. Such methods include the use of mild hydrolysing agents to obtain amides, and stronger hydrolysing agents to obtain the acids, from the nitriles. The amides may also be obtained from the acids or derivatives thereof, such as the acid halides, by reaction with ammonia or an amine. The esters are obtained from the nitriles, acids or amides by means of the appropriate esterifying agent, for which purpose an alcohol or derivative thereof containing a basic group may be used. The ketones are obtained by reacting the nitrile with one of the usual organo-metal compounds, for example, with an alkyl megnesium halide, and decomposing the intermediate product so formed. For the formation of the amines the nitriles are treated with nascent hydrogen or with hydrogen in the presence of a metal catalyst. When α-aryl-α-pyridyl-acetonitriles are used the reaction may be conducted by suitably selecting the reducing agent and the conditions of reduction in such a manner that either a β-aryl-β-pyridyl-ethylamine or a β-aryl-β-piperidyl-ethylamine is obtained. Thus, the piperidine compounds are formed by treatment with hydrogen in the presence of noble metal catalysts, such as platinum, whereas pyridine compounds are formed by treatment with hydrogen in the presence of base metal catalysts, such as nickel. Moreover, in this reduction of the nitriles to amines the secondary bases as well as the primary bases can be obtained according to the conditions used. Thus, for example, β - phenyl - β - pyridyl - (2)-ethylamine and di-(β-phenyl-β-pyridyl-(2) - ethyl) - amine are obtained from α-phenyl - α - pyridyl - (2) - acetonitrile in alcoholic solution by the action of hydrogen at a low temperature in the presence of a nickel catalyst, the presence of ammonia favouring the formation of the primary amine. The primary and secondary ethylamines so obtained can be further substituted in the amino-group by the usual methods, for example, by reaction with formaldehyde in the presence of a reducing agent, such as formic acid, or with an alkyl halide.

The pyridine carboxylic acids or their amides or esters of the invention, and also the pyridyl-ethyl-amines described above may be converted into the corresponding piperidine compounds by the action of reducing agents described in the literature as being suitable for hydrogenating the pyridine nucleus.

The introduction of further substituents at the ring nitrogen atom of the pyridines or piperidines obtained by the present process may be performed at any stage of the reaction. Thus, for example, the corresponding quaternary compounds may be produced by reaction with an alkyl halide, an alkenyl halide, an aryl-sulphonic acid ester, a dialkyl sulphate or an aryl-alkyl halide. It is also possible to obtain tertiary piperidines by starting from piperidines which are unsubstituted at the ring nitrogen atom.

Compounds produced by the present process have valuable physiological properties and are suitable as medicaments or as intermediate products for the production thereof.

The following Examples illustrate the invention:—

EXAMPLE 1.

80 grams of powdered sodamide are slowly added while stirring, and cooling, to a solution of 117 grams of phenyl-acetonitrile and 113 grams of 2-chloro-pyridine in 400 cc. of absolute toluene. The temperature is then gradually raised to 110—120° C. and maintained thereat for one hour. After cooling, the whole is mixed with water, the toluene solution is extracted by agitation with dilute hydrochloric acid, and the acid extracts are rendered alkaline with a concentrated solution of caustic soda. A solid mass separates and is taken up in ethyl acetate and distilled, α - phenyl - α - pyridyl - (2)-acetonitrile passing over at 150—155° C. under a pressure of 0.5 mm. After recrystallisation from ethyl acetate, it melts at 88—89° C. The yield is 135 grams.

In a similar manner there are obtained, starting from 3 - methoxyphenyl - aceto-nitrile and 2 - chloropyridine, α - (3-methoxyphenyl)-α-pyridyl-(2)-acetonitrile melting at 54—55° C.; from 3:4-dimeth-oxyphenyl - acetonitrile and 2 - chloro-pyridine, α - (3:4 - dimethoxyphenyl) - α-pyridyl - (2) - acetonitrile boiling at 192—195° C. under 0.2 mm. pressure; from 3:4 methylene-dioxyphenyl-aceto-nitrile and 2 - chloropyridine, α - (3:4-methylene - dioxyphenyl) - α - pyridyl-(2) - acetonitrile boiling at 170—180° C. under 0.15 mm. pressure; from naphthyl-(1) - acetonitrile and 2 - chloropyridine, α-naphthyl - (1) - α pyridyl - (2) - aceto-nitrile melting at 87° C.; from α-phenyl-α - methyl - acetonitrile and 2 - chloro-pyridine, α-phenyl-α-methyl-α-pyridyl-(2)-acetonitrile boiling at 145—150° C. under 0.2 mm. pressure; from phenyl-aceto-nitrile and 4-chloropyridine, α-phenyl-α-pyridyl-(4)- acetonitrile melting at 76—77° C.; from α-phenyl-α-ethyl-acetonitrile and 4-chloropyridine, α-phenyl-α-ethyl-α-pyridyl-(4)-acetonitrile boiling at 193° C. under 11 mm. pressure; from phenyl-

acetonitrile and N-methyl-3-chloropiperidine, α - phenyl-α-[N-methyl - piperidyl-3)]-acetonitrile boiling at 140—145° C. under 0.2 mm. pressure.

The aforesaid α - phenyl - α - alkyl - α-pyridyl-acetonitriles can also be obtained by alkylating α-phenyl-α-pyridyl-acetonitrile with the appropriate alkyl halides in the presence of sodamide.

100 grams of α-phenyl-α-pyridyl-(2)-acetonitrile are introduced into 400 cc. of concentrated sulphuric acid and allowed to stand for about 15 hours at room temperature, then poured on to ice, and rendered alkaline with solid sodium carbonate. α-Phenyl-α-pyridyl - (2)-acetamide separates, and after recrystallisation from ethyl acetate melts at 134° C. The yield is 96 grams. The corresponding N-methyl - pyridinium metho - sulphate melting at 165° C. is obtained in good yield by treating the product with dimethyl sulphate in alcohol on the water bath.

100 grams of the α-phenyl-α-pyridyl-(2)-acetamide so obtained are dissolved in 1 litre of methyl alcohol, and treated with hydrogen chloride for 6 hours at the temperature of the water bath. After concentration, dilution with water, and being rendered alkaline with solid sodium carbonate, a yield of 90 grams of α-phenyl-α-pyridyl-(2)-acetic acid methyl ester is obtained. It melts at 74—75° C. after recrystallisation from aqueous ethyl alcohol of 50 per cent strength. By esterification in the presence of ethyl alcohol the corresponding α - phenyl - α-pyridyl-(2)-acetic acid ethyl ester boiling at 155—160° C. under 0.4 mm. pressure is obtained in a similar manner.

The same esters can also be obtained by dissolving the α-phenyl-α-pyridyl-(2)-acetonitrile directly in the appropriate alcohol, instead of the amide, and applying the same treatment with hydrogen chloride at the temperature of the water bath.

By hydrogenating 50 grams of α-phenyl-α-pyridyl-(2)-acetic acid methyl ester in glacial acetic acid at room temperature in the presence of 1 gram of a platinum catalyst there is obtained, after the absorption of 6 atoms of hydrogen, a theoretical yield of α-phenyl-α-piperidyl-(2)-acetic acid methyl ester boiling at 135—137° C. under 0.6 mm. pressure. The N-methyl derivative obtained by heating with aqueous formaldehyde and formic acid on a water bath, boils at 153° C. under 0.4 mm. pressure.

α-Phenyl - α - piperidyl - (2) - acetic acid ethyl ester may also be obtained in the following manner: By hydrogenating α-phenyl-α-pyridyl-(2)-acetamide also with a platinum catalyst the corresponding α-phenyl - α - piperidyl - (2) - acetamide is obtained, of which the acetate melts at 158° C. after recrystallisation from ethyl acetate. By saponification with boiling hydrochloric acid the resulting product yields α-phenyl-α-piperidyl-(2)-acetic acid hydrochloride decomposing at 248° C. Esterification with methyl alcohol furnishes the aforesaid ester The corresponding ethyl ester forms a hydrochloride melting at 173° C. and an N-methyl derivative boiling at 138—140° C. under a pressure of 0.4 mm. The *n*-propyl ester forms a hydrochloride melting at 181° C., and an N-methyl derivative boiling at 140° C. under a pressure of 0.3 mm.

The following amides and esters, obtained in a similar manner, may also be mentioned:

α-phenyl-α-pyridyl-(4)-acetamide melting at 154° C.;

α - phenyl - α - pyridyl - (2) - α - methyl-acetamide melting at 130° C.;

α - phenyl - α - pyridyl - (2) - α - ethyl-acetamide melting at 108° C.;

α - phenyl - α - piperidyl - (2) - α - ethyl-acetamide melting at 151—152° C.;

α - phenyl - α - pyridyl - (4) - acetic acid methyl ester boiling at 150° C. under 0.2 mm. pressure;

α - phenyl - α - piperidyl - (4) - acetic acid methyl ester boiling at 145° C under 0.2 mm. pressure;

α - phenyl - α - N - methylpiperidyl - (4)-acetic acid methyl ester melting at 63° C.;

α - phenyl - α - pyridyl - (2) - acetic acid β - diethylaminoethyl - ester boiling at 160—163° C. under 0.2 mm. pressure;

α - phenyl - α - piperidyl - (2) - acid β-diethylaminoethyl ester hydrochloride melting at 170° C.

EXAMPLE 2.

A solution of 90 grams of the α-phenyl-α-ethyl-α-pyridyl-(4)-acetonitrile described in Example 1 in 200 cc. of anisole is introduced at 50—60° C. into a solution of *n*-propyl - magnesium - bromide, prepared from 70 grams of *n*-propyl bromide and 12 grams of magnesium, in 200 cc. of 12 grams of magnesium, in 200 cc. of anisole. When the reaction, which is accompanied by a slight liberation of heat, has subsided, the mixture is heated at 60—70° C. on the water bath for a further 2 hours. It is then cooled, and the organo-metal compound formed is decomposed with ice-water and 2 N hydrochloric acid. The anisole solution is shaken twice with dilute hydrochloric acid, the base is precipitated from the united hydrochloric acid extracts, and is taken up in ether. After drying the ethereal solution with potassium carbonate, followed by distillation, 80 grams

of α-phenyl-α-pyridyl-(4)-di-*n*-propyl ketone are obtined, in the form of an oil boiling at 110—115° C. under 0.15 mm. pressure.

In an analogous manner α-phenyl-α-pyridyl-(2)-diethyl ketone melting at 74° C. is obtained from α-phenyl-α-methyl-α-pyridyl-(2)-acetonitrile and ethyl-magnesium-bromide; and [α-phenyl-α-pyridyl-(2)-ethyl]-*n*-propyl ketone melting at 55° C. from α-phenyl-α-methyl-α-pyridyl-(2)-acetonitrile and *n*-propyl-magnesium-bromide.

EXAMPLE 3.

20 grams of the α-phenyl-α-pyridyl-(2)-acetonitrile described in Example 1 are dissolved in 150 cc. of absolute ethyl alcohol and reduced at 60—70° C. with hydrogen in an autoclave in the presence of 5 grams of a nickel catalyst. When the calculated quantity of hydrogen (4 atoms) for the reduction of the —CN-group has been absorbed, the pressure ceases to fall. After removing the catalyst by filtering with suction, and evaporating the solution, an oily substance is obtained from which 10 grams of the acetate of the primary base, β-phenyl-β-pyridyl-(2)-ethylamine, is precipitated by admixture with 200 cc. of ethyl acetate and 4 cc. of glacial acetic acid. The acetate melts at 124° C., and the base liberated therefrom boils at 130° C. under a pressure of 0.15 mm. The hydrochloride melts at 210—211° C. The ethyl-acetate filtrate is evaporated, and the residue is mixed with 2 N caustic soda solution and taken up in ether. The ethereal residue consists of about 10 grams of the crude secondary base, di-[β-phenyl-β-pyridyl-(2)-ethyl]-amine. It melts at 84—85° C. after recrystallisation from ether; the hydrobromide melts at 140° C., and the picrate at 179—180° C.

The following amines are prepared in an analogous manner: β-(3-methoxyphenyl)-β-pyridyl-(2)-ethylamine, of which the hydrochloride melts at 210—211° C., and di-[β-(3-methoxyphenyl-β-pyridyl-(2)-ethyl]-amine, of which the picrate melts at 145° C., both obtained from α-(3-methoxyphenyl)-α-pyridyl-(2)-acetonitrile; and β-phenyl-β-pyridyl-(4)-ethylamine, of which the hydrochloride melts at 199° C., and di-[β-phenyl-β-pyridyl-(4)-ethyl]-amine, of which the picrate melts at 187° C., both obtained from α-phenyl-α-pyridyl-(4)-acetonitrile.

The formation of the primary bases is favoured by hydrogenating the nitriles in the presence of ammonia. Thus, for example, there can be obtained β-phenyl-β-pyridyl-(4)-β-ethylamine (boiling at 130—135° C. under 0.2 mm. pressure), β-naphthyl-(1)-β-pyridyl-(2)-ethylamine or β-methylene-dioxyphenyl-β-pyridyl-(2)-ethylamine.

Derivatives of the aforesaid amines may be prepared. For example, from β-phenyl-β-pyridyl-(2)-ethylamine by hydrogenation with hydrogen in the presence of a platinum catalyst β-phenyl-β-piperidyl-(2)-ethylamine, of which the acetate melts at 99° C., and di-[β-phenyl-β-piperidyl-(2)-ethyl]-amine melting at 82° C., can be obtained; by condensation with formaldehyde in the presence of formic acid β-phenyl-β-pyridyl-(2)-ethyl-dimethylamine, of which the hydrochloride melts at 190° C., can be obtained; by condensation with 1 mol. of formaldehyde and hydrogenating the resulting Schiff's base and the pyridine nucleus with hydrogen in the presence of a platinum catalyst, β-phenyl-β-piperidyl-(2)-ethyl-monomethylamine boiling at 147—152° C. under 0.1 mm. pressure can be obtained; by condensation with benzoldehyde and hydrogenation at 20° C. β-phenyl-β-pyridyl-(2)-ethyl-benzylamine can be obtained; by condensation with benzaldehyde and hydrogenation at 60—70° C. β-phenyl-β-piperidyl-(2)-ethyl-benzylamine can be obtained; by condensation with pyridyl-(3)-aldehyde and hydrogenation of the Schiff's base β-phenyl-β-pyridyl-(2)-ethyl-[pyridyl-(3)-methyl]-amine boiling at 190—195° C. under 0.25 mm. pressure can be obtained; by reaction with cyanamide β-phenyl-β-pyridyl-(2)-ethyl-guanidine, of which the acetate melts at 202° C., can be obtained; and from other amines the corresponding derivatives can be obtained.

Having now particularly described and ascertained the nature of our said invention and in what manner the same is to be performed, we declare that what we claim is:—

1. A manufacture of new pyridine or piperidine compounds by condensing a monoaryl-acetonitrile containing at least one hydrogen atom in the acetonitrile-residue with a pyridine or piperidine compound halogenated in the nucleus, in the presence of a metal or metal compound capable of eliminating halogen hydride, and, if desired, replacing by an alkyl residue a hydrogen atom attached to the carbon atom to which the nitrile group is connected.

2. A manufacture as claimed in claim 1, wherein the nitrile group in an α-aryl-α-pyridyl-acetonitrile or an α-aryl-α-piperidyl-acetonitrile obtained in the process is converted in one or more stages into a carboxyl group by a known method as hereinbefore defined.

3. A manufacture as claimed in claim 1, wherein the nitrile group in an α-aryl-α-pyridyl-acetonitrile or an α-aryl-α-piperidyl-acetonitrile obtained in the process is converted in one or more stages into an ester group by a known method as hereinbefore defined.

4. A manufacture as claimed in claim 1, wherein the nitrile group in an α-aryl-α-pyridyl-acetonitrile or an α-aryl-α-piperidyl-acetonitrile obtained in the process is converted in one or more stages into an amide group by a known method as hereinbefore defined.

5. A manufacture as claimed in claim 1, wherein the nitrile group in an α-aryl-α-pyridyl-acetonitrile or an α-aryl-α-piperidyl-acetonitrile obtained in the process is converted into a keto group by a known method as hereinbefore defined.

6. A manufacture as claimed in claim 1, wherein the nitrile group in an α-aryl-α-pyridyl-acetonitrile or an α-aryl-α-piperidyl-acetonitrile obtained in the process is converted in one or more stages into a methylene-amino group by a known method as hereinbefore defined.

7. A manufacture as claimed in claim 2 or 4, wherein the α-aryl-α-pyridyl-acetonitrile or α-aryl-α-piperidyl-acetonitrile is treated with a hydrolysing agent.

8. A manufacture as claimed in claim 3 and claim 1, 2, 4 or 7, wherein an α-aryl-α-pyridyl-acetonitrile or an α-aryl-α-piperidyl-acetonitrile or a corresponding acid or acid amide obtained in the process is treated with an esterifying agent.

9. A manufacture as claimed in claim 5, wherein the α-aryl-α-pyridyl-acetonitrile or α-aryl-α-piperidyl-acetonitrile is reacted with an alkyl magnesium halide and the intermediate product so formed is then decomposed.

10. A manufacture as claimed in claim 2, 3, 4, 7 or 8, wherein a pyridine compound obtained in the process is treated with a reducing agent described in the literature as being suitable for hydrogenating the pyridine nucleus.

11. A manufacture as claimed in claim 1, wherein an α-aryl-α-pyridyl-acetonitrile or an α-aryl-α-piperidyl-acetonitrile obtained in the process is treated with hydrogen in the presence of a catalyst.

12. A manufacture as claimed in claim 11 wherein the α-aryl-α-piperidyl-acetonitrile is treated with hydrogen in the presence of a platinum catalyst.

13. A manufacture as claimed in claim 11, wherein the α-aryl-α-piperidyl-acetonitrile is treated with hydrogen in the presence of a nickel catalyst.

14. A manufacture as claimed in claim 13, wherein the α-aryl-α-piperidyl-acetonitrile is treated with hydrogen in the presence of a nickel catalyst and ammonia.

15. A manufacture as claimed in claim 1, wherein phenyl-acetonitrile is condensed with a 2-halogen-pyridine in the presence of sodamide.

16. A manufacture as claimed in claim 15, wherein the α-phenyl-α-pyridyl-(2)-acetonitrile obtained in the process is esterified and the α-phenyl-α-pyridyl-(2)-acetic acid ester so obtained is then treated with hydrogen in the presence of a platinum catalyst.

17. A manufacture as claimed in claim 15, wherein the α-phenyl-α-pyridyl-(2)-acetonitrile obtained in the process is hydrolysed to produce α-phenyl-α-pyridyl-(2)-acetic acid amide, which is then treated with hydrogen in the presence of a platinum catalyst, and the α-phenyl-α-piperidyl-(2)-acetic acid amide so obtained is esterified.

18. A manufacture as claimed in any one of claims 1—17, wherein, at any stage of the process, a further substituent is introduced at the ring nitrogen atom of the pyridine or piperidine compound by treating the said compound with an alkyl halide, an alkenyl halide, an aryl-sulphonic ester, a dialkyl sulphate or an aryl-alkyl halide.

19. A manufacture of a new pyridine or piperidine compound conducted substantially as described in any one of the Examples herein.

20. Pyridine or piperidine compounds whenever prepared or produced by the process of manufacture particularly described and ascertained herein or by any process which is an obvious chemical equivalent thereof.

Dated this 18th day of January, 1945.

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